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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/725,540	10/03/96	BRASEL	K 2836-A

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EXAMINER	
VANDER VEGT,F	
ART UNIT	**PAPER NUMBER**
1644	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/725,540	Applicant(s) Brasel et al
	Examiner F. Pierre VanderVegt	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Feb 22, 1999* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-19* is/are pending in the application.

Of the above, claim(s) *6-19* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The request filed on February 22, 1999 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/725540 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-19 are currently pending in this application.

Claims 6-19 stand withdrawn, as being drawn to a non-elected invention.

Accordingly, Claims 1-5 are currently under examination.

1. The Examiner in charge of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner F. Pierre VanderVegt in Group Art Unit 1644.

Priority

2. If Applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant specification. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. Reference to the parent application Serial Number 08/539,142 was made in the oath; however, all parent applications as well as an update of their status must be in the specification. Correction is required.

3. The incorporation of essential material by reference to a foreign application or foreign patent or to a publication inserted in the specification on Page 4 is improper. Incorporation of the information in U.S. Patent 5,554,512 is proper. If the information in U.S. Patent 5,554,512 is not sufficient to provide the required information for making flt3-ligand and if Applicant must therefore rely on EP 0627487 A2 or WO 94/28391, Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must

be accompanied by an affidavit or declaration executed by the Applicant, or a practitioner representing the Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 112

4. Claims 1- 5 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The specification fails to provide any guidance for enhancing a lymphocyte-mediated immune response in a patient comprising administering an amount of flt3-ligand to a patient sufficient to generate an increase in the number of the patient's dendritic cells. The specification discloses that "an effective amount of flt3-L can be used to increase or mobilize the numbers of dendritic cells *in vivo*", that "by increasing the quantity of the patient's dendritic cells, such cells may themselves be used to present antigen to T cells", and that "the antigen may be one that already exists within the patient, such as a tumor antigen". Thus, the specification discloses that flt3-L can be used as an adjuvant enhancing a patient's overall immune response (Paragraph bridging Pages 9 and 10). An *in vivo* example is presented wherein flt3-ligand administered to mice with tumors results in the augmentation of an anti-tumor immune response. However, there is no teaching indicating that administering flt3-L alone *in vivo* results in a differentiation step as well as an increased number of dendritic cells. Although pharmaceutical formulations and dosages are disclosed (Page 12), there is no *in vivo* exemplification for treating infectious diseases. There is no teaching indicating that administering flt3-L alone or together with any of the other recited cytokines *in vivo* results in a differentiation step as well as an increased number of dendritic cells; that the generated,

expanded dendritic cells would present any antigen of interest, or, in particular, that they would present viral antigens or other antigens specific to an infectious disease; and that such "pulsed" dendritic cells would find themselves in the appropriate, targeted microenvironment so that an enhancing effect on any lymphocyte-mediated immune response or in particular, on any anti-viral response or on any immune response important in infectious disease, could be measured.

There is insufficient guidance to direct a person of skill in the art to know, for example, (1) the critical steps required for enhancing an immune response or an anti-viral response or an anti-infectious agent response and (2) the criteria and values expected for determining that an immune response had been enhanced based on the effect of flt3-L on the generation and expansion of dendritic cells. There is insufficient guidance to direct one to know how to measure that there *has* been an increase in the number of a patient's dendritic cells (Claim 1). There is no teaching or written description of how an *in vivo* increase in dendritic cells can be measured if the dendritic cells are "pulsed *in vivo*" with a viral antigen or bacterial antigen located either at a target site or in the circulation. A person of skill in the art could not predict that administering flt3-L *in vivo* would result in mobilization/differentiation of dendritic cells, expansion of dendritic cells, and *in vivo* presentation of viral or bacterial antigens, with the result being a therapeutic effect on infectious disease, without undue experimentation. The *ex vivo/in vitro* expansion of dendritic cells as exemplified does not accurately reflect the relative efficacy of the claimed therapeutic strategies against infectious diseases wherein flt3-ligand is administered *in vivo*, alone or together with other lymphokines. Thus, there is insufficient objective evidence commensurate in scope with the therapeutic methods encompassed by the claimed methods.

Pharmaceutical therapies are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, *i.e.*, such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, *i.e.*, the protein may not be able to cross the mucosa or

the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, *i.e.*, adverse side effects prohibitive to the use of such treatment. See Page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat. App. & Inter. 1992).

It has been well known in the art that retroviral infections in general and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: (1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; (2) the fact that modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; (3) the existence of a latent form of the virus; (4) the ability of the virus to evade immune response in the central nervous system due to the blood-brain barrier; and (5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation.

There is insufficient guidance and direction as to the desired therapeutic endpoints for the claimed method to augment the immune response in patients with infectious disease. In not setting forth the nature or function which is to be achieved in the instant methods, Applicant has not therefore set forth how to use the instant methods.

In view of insufficient guidance by the instant specification and the lack of predictability of the art to which the invention pertains with respect to the treating of HIV infected individuals and the *in vivo* therapeutic modalities via flt3-ligand, undue experimentation would be required to practice the claimed immunotherapeutic methods to achieve an effective treatment of HIV infected individuals with *in vivo* administered flt3-ligand with a reasonable expectation of success, absent a specific and detailed description in

Applicant's specification and absent working examples providing evidence for achieving a therapeutic end result reasonably predictive for treating HIV infected individuals by administering flt3-ligand commensurate in scope with the claimed invention.

U.S. Patent 5,627,025 to Steinman *et al.*(A on form PTO-892, of record) teach that dendritic cells are important for the production of HIV virions *in situ*. The '025 patent teaches that dendritic cells that are bone marrow-derived, localized to the T cell area of lymphoid organs, and specialized in many ways to present processed antigens to both CD4+ and CD8+ T cells are of interest because experimentally, the major site for productive infection with HIV-1 is the stimulated CD4+ T cells. The '025 patent also teaches that when human blood dendritic cells are pulsed with HIV-1 and then present antigen in this microenvironment, the dendritic cells are not infected, but virus is efficiently transferred to the responding T cells (Column 2, Lines 28-50, in particular). The '025 patent further teaches that"contact of memory T cells with infected dendritic cells, which may act as a reservoir for HIV infectivity, fosters chronic HIV infection. Contact of memory T cells with HIV infected dendritic cells may also provide a mechanism for the infection of these important immune cells, and explains the persistent elimination of CDR-positive T lymphocytes characteristic of HIV infection (Column 4, Lines 49-57, in particular). The Sprecher et al reference (U, of record) teaches HIV-1 replication in dendritic cells and Langerhans cells. Sprecher et al teaches that "HIV-1 was even shown to replicate more efficiently in dendritic cell cultures than in monocyte or CD4+ T cell cultures" (Page 12, Paragraph 1, in particular). Sprecher et al also teaches that "HIV DNA was also detected in (a) dendritic cells isolated from the peripheral blood of HIV-infected patients; (b) dendritic cells separated from the synovial fluid of seropositive patients with arthritis, and (c) dendritic cells microdissected from heart muscle biopsies obtained from AIDS patients (Page 13, Paragraph 2, in particular). Therefore, it is clearly not predictable that increasing the number of dendritic cells in HIV-infected individuals will lead to an enhanced immune response.

There is insufficient guidance and *in vivo* exemplification to enable one of skill in the art to predictable augment the immune response of an individual by administering flt3-ligand *in vivo* together with other known cytokines. The results of administering cytokines *in vivo* as antagonists or agonists is unpredictable. Debets et al (V, of record) teaches that soluble cytokine receptors can act as antagonists or agonists, "thereby acting as 'double edged swords'" (Page 456, Column 3, in particular).

Without guidance and working examples, the scope of the claims encompassing all infectious diseases cannot be supported. The level of skill in the art is high; however, the unpredictability in the art is high. Therefore, sufficient guidance and description is required to overcome the unpredictability encompassed by the scope of Applicant's claims and to provide sufficient guidance for a person of skill in the art to use the claimed invention without undue experimentation. Factors to be considered in determining scope and enablement are: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (see *Ex parte Forman*, 230 USPQ 546, BPAI, 1986). Thus, there is insufficient guidance to enable a person of skill in the art to predictably treat all individuals with all infectious diseases using the claimed methods.

In view of the lack of predictability of the art to which the invention pertains and the limited working examples, the state of the prior art, the lack of guidance in the specification and the breadth of the claims, it would take undue experimentation to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1- 5 stand rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent 5,635,388 to Bennett et al (B) in view of Broxmeyer et al (W) and Porgador et al (X), all of record.

The '388 patent teaches that agonist antibodies specific for flt3 receptor are capable of causing primitive hematopoietic (CD34+) cells to proliferate and differentiate and thereby enhance repopulation of mature blood cell lineages the growth, proliferation or differentiation of progenitor cells and stem cells (Columns 20-23). The '388 patent also teaches that the agonist antibodies specific for flt3 receptor have similar properties to the flt3-ligand of Lyman (Columns 3 and 4, in particular). The '388 patent teaches use of the agonist antibodies together with GM-CSF, IL-3, IL-4, kit-ligand and TNF. Using the compositions of the '388 patent results in the generation of dendritic cells. Broxmeyer et al teaches the potent stimulatory effects of flt3-L on myeloid stem/progenitor cells. The combination of the '388 patent and Broxmeyer et al does not specifically teach *in vivo* administration of agonist antibodies specific for flt3 or flt3-ligand to treat infectious disease. However, Porgador et al teaches that dendritic cells are capable of inducing antigen-specific CD8+ T cell responses *in* vivo. Porgador et al teaches, and the art recognized, that CD8+ CTL responses play an important role in many infectious diseases and that their results provide a rationale for using bone-marrow -generated dendritic cells in CTL-mediated immunotherapy of infectious diseases. The *in vitro*

differentiation of CD34+ cells to become dendritic cells in the presence of GM-CSF and IL-3 was well known in the art at the time of the invention. Thus, the administration of lymphokines to induce the differentiation of precursor cells to dendritic cells both *in vivo* and *in vitro* was known. The resulting differentiated dendritic cells would then serve as antigen presenting cells for the *in vivo* activation of T cells specific for the antigen being presented. The activation of antigen-specific T cells results in their becoming antigen-specific effector cells that are cytotoxic T cells specific for viral antigens, for example. It is recognized in the art that cytotoxic T cells secrete lymphokines; therefore, such anti-viral cytotoxic T lymphocytes would have similar capabilities to secrete lymphokines that also contribute to the immunomodulatory response. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the flt3-ligand taught by Broxmeyer et al for the agonist antibodies of the '388 patent and to administer the flt3-ligand to patients with infectious diseases as taught by Porgador et al in order to stimulate the differentiation of dendritic cells *in vivo* and thereby treat infectious diseases. Such dendritic cells would then present antigen *in situ* to antigen-specific T cells and thus activate them to become activated effector cells capable of modulating an immune response. Based on the teachings of the references, one of ordinary skill in the art would have a reasonable expectation of success in producing the claimed effects. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

7. All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office Action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1644 is (703)305-3014.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Tuesday through Friday and even-numbered Mondays (on 1999 365-day calender) from 7:00 am to 4:00 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.

April 27, 1999
F. Pierre VanderVegt, Ph.D.
Patent Examiner, Art Unit 1644

David A. Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644